TREATMENT OF PROSTATIC CANCER: STUDIES BY THE VETERANS ADMINISTRATION COOPERATIVE UROLOGICAL RESEARCH GROUP*

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MANY of you have already become familiar with some of the results of the studies of treatment for cancer of the prostate made by the Veterans Administration Cooperative Urological Research Group.[1-4] Indeed, this study has been a subject of controversy and has attracted many critics as well as admirers. It is understood that our studies indicate that treatment of prostatic cancer with estrogen is not indicated and may even be harmful. This is true in part, but many misunderstandings have arisen from this oversimplified view. Actually there have been three consecutive studies of treatment for cancer of the prostate. Patients are still being followed in all of them. In the first study patients were admitted from 1960 until 1967, in the second study, from 1967 until 1969, and they are still being admitted in the third study. Table I shows the admission of patients in all three studies from 1960 until last March. The average admission of new patients is about 300 per year. It is my purpose here to review the first two studies, to describe the design and operation of the studies, to present the most recent data, and to allow you to draw your own conclusions in light of the evidence thus far obtained.

The Veterans Administration Cooperative Urological Research Group (VACURG) was organized in 1960. The original group consisted of 14 V.A. hospitals, all of which had full-time urologists on their staffs at that time. The purpose of the group was to conduct large-scale, prospective, statistically randomized clinical trials of treatment of urologic disorders. The main effort was directed to a study of the common treatments then in use for cancer of the prostrate, since

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TABLE I. PATIENTS ADMITTED PER YEAR TO THE VACURG PROSTATE STUDIES

Year	*No. of patients*	*Study*
1960	149	
1961	264	
1962	380	
1963	385	
1964	422	I
1965	383	
1966	289	
1967	42	
1967	186	
1968	274	II
1969	101	
1969	151	
1970	255	III
1971*	151	
All years	3,432	

* Through July 1971

there was no general agreement about the best way to treat these patients: that is, whether to use estrogen or orchiectomy, or both, and when these treatments could best be employed. The role of radical prostatectomy for the early lesions was also to be studied.

I think it is useful to emphasize that although other cooperative groups had studied this problem and other large series had been reported, none of these was statistically randomized, properly controlled, or even prospective in design. The V.A. study then, so far as I am aware, was the first large-scale randomized clinical trial of treatment for this disease.

In all the VACURG studies all new patients with cancer of the prostate are considered for study. However, only those may be admitted who have a positive histological diagnosis of prostatic cancer, who have not received previous hormonal or surgical treatment for their cancer, who have no other malignancy, and who can withstand treatment selected by randomization. In the seven-year period of Study I, 3,793 patients were considered and 1,479 (or about 39%) were excluded for various reasons (Table II). The principal reasons, as you can see, are

TABLE II. REASONS FOR REJECTION FROM PROSTATE STUDY I

Reason rejected	*Number*	*No. of all rejects*
Previous treatment	668	45.2
Physical condition	403	27.2
Second malignant lesion	229	15.5
Psychotic, senile	64	4.3
Refused study treatment	51	3.5
Expired during pretreatment	22	1.5
Miscellaneous	42	2.8
All reasons	1,479	100.0

previous treatment, physical condition, and second malignant lesions. If those previously treated are excluded, then about 75% of new patients were eligible for admission to Study I. In our studies patients are assigned to one of four stages according to a system generally accepted by most authorities (Figure 1). This system is based on clinical and laboratory information available to the urologist before he begins treatment of the patient; thus information obtained at open operation about the degree of spread of the tumor is not used. There are four stages: I—tumor confined to the prostate and not detectable by rectal examination. In this stage tumors are diagnosed as incidental findings either by routine needle biopsy or by pathological examination of tissue removed transurethrally for benign obstructive disease. Stage II tumors are still confined to the prostate gland, but they are detectable by rectal examination. This stage includes the so-called "prostatic nodules." Stage III tumors are locally extended, and stage IV tumors have distant metastases, as evidenced by either biopsy, radiographic findings, or an elevated acid phosphatase, defined as greater than 1.0 K.A.U.

In order to standardize the staging procedure, all biopsies were sent to Dr. F. K. Mostofi at the Armed Forces Institute of Pathology for examination and all acid-phosphatase determinations were performed in a central laboratory under the direction of Dr. Richard P. Doe. The protocol specified that all rectal examinations used in determinations of stage and at the follow-up visits were to be performed by the principal investigator at each participating institution. Finally, x-ray findings that were questionable were to be submitted to a referee radiologist, Dr. Joseph Jorgens, for final decision.

STAGE	RECTAL EXAMINATION	PROSTATIC ACID PHOSPHATASE	X-RAY OR BIOPSY EVIDENCE OF METASTASES
I	NO INDURATION	≤1.0 K.A.U.	0
II	LOCALIZED NODULE	≤1.0 K.A.U.	0
III	EXTRA-PROSTATIC EXTENSION	≤1.0 K.A.U.	0
IV	EQUIVOCAL FINDINGS	>1.0 K.A.U. OR	+

Fig. 1. Staging system used in the VACURG studies of cancer of the prostate.

TABLE III. NUMBER OF PATIENTS BY STAGE IN THE THREE MAIN V.A. PROSTATE STUDIES

	Study I		*Study II*		*Study III*	
Stage	*Number*	*% of total*	*Number*	*% of total*	*Number*	*% of total*
I	120	5.2	32	5.7	17	3.9
II	179	7.7	21	3.7	30	6.9
III	1,105	47.8	294	52.4	201	46.0
IV	910	39.3	214	38.2	189	43.2
All stages	2,314	100.0	561	100.0	437	100.0

Altogether, 2,314 patients were admitted to the study. Table III shows the distribution of patients by stage in all three main studies.

The treatments chosen for the first V.A. study were the following: for stages I and II, radical prostatectomy and placebo, or radical prostatectomy and 5.0 mg. diethylstilbestrol (DES) daily; for stages III and IV, random assignment to one of the following four treatments: placebo, 5.0 mg. DES, orchiectomy and placebo, or orchiectomy and 5.0 mg. DES, all drugs administered daily.

The protocol stated that the clinician was to be free to change the treatment of any patient whose welfare he thought indicated the need for a change, but the statistical office was to be informed of all such changes and these patients were to be followed regularly according to the protocol as were the patients who were still receiving the assigned treatment.

There were two reasons for this provision: first, our goal was not to measure the growth or regression of tumors in isolation from the response of other organ systems or apart from the clinical setting in

which the patient was being followed. Instead we were attempting to determine how patients should be treated in practice. No two patients are ever in quite the same condition when first seen, and no two will have identical clinical courses; therefore the practicing urologist adapts his management of each case to fit the needs of the patient. This will continue to be the case with any treatment recommended after a clinical trial such as this study. Thus on practical as well as ethical grounds we felt that the urologists participating in the study should be allowed some degree of personal discretion in the treatment of their patients. Hence not all patients were treated in exactly the same way. The second reason is that any attempt to exclude from the analysis patients whose treatments were later changed would result in a bias indicating increased survival for the worst treatments since the sicker patients would have been removed from those groups. Thus, strictly interpreted, our results are meant to apply to initially assigned treatment with the understanding that treatment may be changed later at the discretion of the clinician if indicated.

Table IV shows the status of this study as of September 1971 when the study was most recently brought up to date by further follow-up. This is done every six months. This table shows the causes of death by stage and treatment for the patients in all stages. Looking first at the causes of death for Stage III, we see that there are excess cancer deaths among patients who were treated with placebo or placebo and orchiectomy, but there are excess cardiovascular deaths in those who were treated either with estrogen alone or with the combination of estrogen and orchiectomy. The pattern is not quite so clear in the data for stage IV, but it is apparent in stages I and II.

Looking now at the total deaths in stage III, we see that there were somewhat fewer deaths in those who were not treated with estrogen. One cannot draw firm conclusions from a table such as this because it contains no information as to when the deaths occurred. Clearly, if you treat two groups of patients differently and then follow them long enough, all patients in both groups will eventually die, but you would not want to conclude that the two treatments were therefore equivalent in their effect on mortality. You would want to know in which group most of the patients died first. For this reason we use actuarial survival curves to compare treatments. This information, combined with the data on specific causes of death, forms a basis for comparing treatments.

TABLE IV. DEATHS BY STAGE, TREATMENT, AND CAUSE OF DEATH IN PROSTATE STUDY I

Stage	*III*				*IV*			
Treatment	*Placebo*	*Estrogen*	*Orch. + placebo*	*Orch. + estrogen*	*Placebo*	*Estrogen*	*Orch. + placebo*	*Orch. + estrogen*
Number of patients	262	265	266	257	223	211	203	216
CA of prostate	46	17	34	22	102	78	93	81
Cardiovascular	82	103	84	102	55	72	54	58
Other causes	37	46	43	43	26	21	27	37
Total deaths	165	166	161	167	183	171	174	176

TABLE V. CARDIOVASCULAR AND OTHER DEATHS BY PRETREATMENT DISEASE CATEGORIES, STAGES I AND II IN PROSTATE STUDY I*

Assigned Tx:	*Prostatectomy + placebo*				*Prostatectomy + estrogen*				
Disease Hx:	*None*		*Cardiovascular*	*All other*	*None*		*Cardiovascular*	*All other*	*Total*
Number of patients	75		37	33	74		44	36	299
Cancer of prostate	3		6	0	0		1	0	10
Heart or vascular	6		6	3	9		10	5	39
Cerebrovascular	4	14.7%	2	21.6% 1	12.1%	4	20.3% 6	45.5% 2	25.0% 19
Pulmonary embolus	1		0	0	2		4	2	9
Other cancer	3		0	6	2		0	0	11
Respiratory	2		0	0	0		1	1	4
All other + unknown	1		1	1	2		1	3	9
Alive	55		22	22	55		21	23	198

*As of April 1970

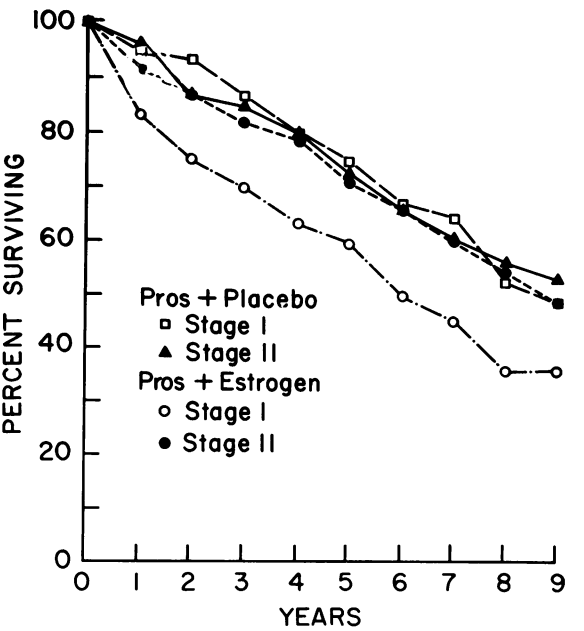

Fig. 2. Prostate study I: survival curves by assigned treatment for stages I and II.

Survival curves for stage I are shown in Figure 2.* If one imagines averaging the survival for the two solid lines (Stage I) you can see that, contrary to what you might expect, Stage I patients do not survive as long as Stage II patients, whose lesions are presumably more advanced. We think this is due to the manner in which these lesions are diagnosed: namely, the patient is already having trouble, usually benign obstruction, which causes him to consult his physician. Among patients in Stage II, on the other hand, the disease is almost by definition detected by routine physical examination of presumably healthy persons. When statistical tests are applied to these curves, they indicate that placebo is significantly better than 5.0 mg. DES in Stage I. There is no significant difference in Stage II.

In Figure 3 we see survival curves for Stage III. One's immediate impression on looking at these curves is that there is very little difference between them; this seems to contradict the impression derived from the table of causes of death. There was some difference there in favor of those treated with placebo and placebo plus orchiectomy. One must remember, however, that we are dealing with relatively large groups of

*Unless otherwise stated, all survival curves are for all causes of death combined.

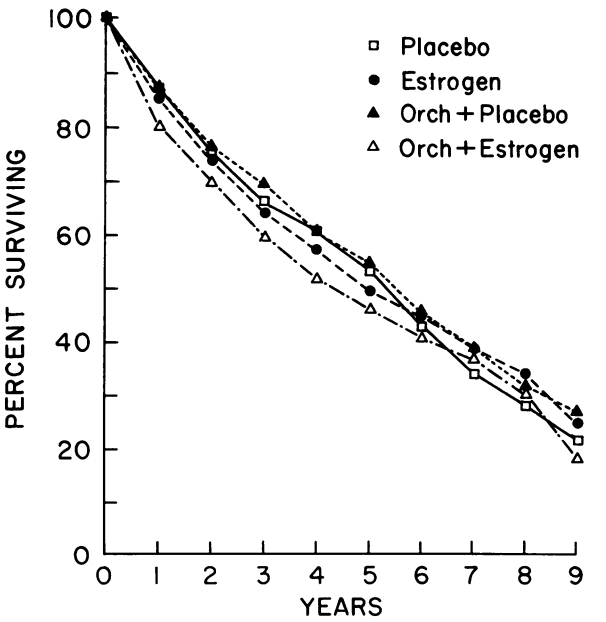

Fig. 3. Prostate study I: survival curves by assigned treatment for Stage III.

patients. About 260 patients are represented by each curve. Survival curves based on small numbers of patients may look quite different and need not be statistically significant. The reverse is also true: small differences in curves based on large numbers of patients may be statistically significant. And that is the case here. When statistical tests[5] were applied, we found that placebo and placebo plus orchiectomy are significantly better than estrogen plus orchiectomy. No other comparisons are significant at any time. One might say, however, that even though the differences are statistically significant, they are not very large or very important in the clinical sense, but again we must remember that these curves represent large groups of patients and that even small differences may denote appreciable numbers of deaths. I do not think one would choose to use a treatment that resulted in even 10 more deaths among 250 patients. If these comparisons were not made within a randomized study, one might choose to ignore these differences, but here I think we are compelled to take them seriously.

The survival curves for Stage IV are shown in Figure 4. Here statistical tests[5] show no significant differences.

Since we have become aware of the cardiovascular hazards of estro-

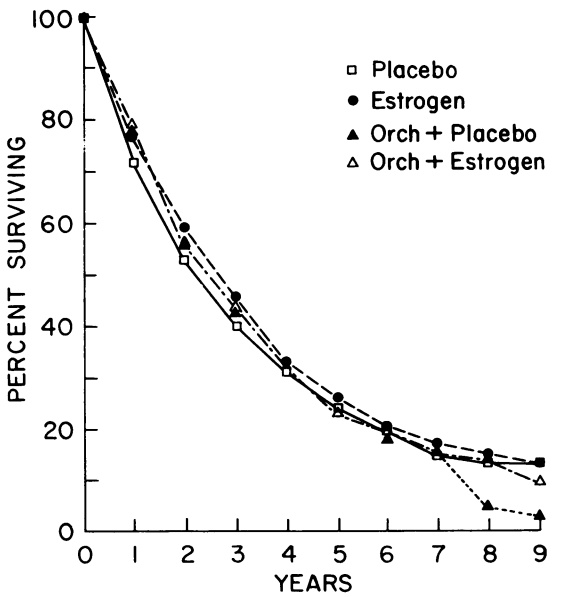

Fig. 4. Prostate study I: survival curves by assigned treatment for Stage IV.

gen in treating some of these patients, we have tried to look at the problems in various ways in an effort to select those patients who might be especially susceptible to this hazard. Dr. Clyde Blackard of the Minneapolis V.A. Hospital has reviewed the clinical charts of all patients in our study from his hospital and has found that a history of cardiovascular disease is a predisposing factor.[6] We have reviewed the pretreatment cardiovascular histories of all the Stage I and II patients in the study and found the same thing (Table V): cardiovascular death was much more common in patients with a previous history of cardiovascular disease.

When I say "cardiovascular disease" or "cardiovascular deaths" I am referring to myocardial infarction, cerebrovascular accidents, congestive heart failure, arteriosclerotic heart disease, and pulmonary embolism. We have not usually found it useful to divide these causes into the separate diagnostic categories. But because of the recent publicity concerning the increased risk of pulmonary embolism in young women taking the contraceptive pill, I have plotted the cumulative deaths from pulmonary embolism for a seven-year period for the patients in Stages III and IV of Study I (Figure 5). Clearly the major hazard occurs in

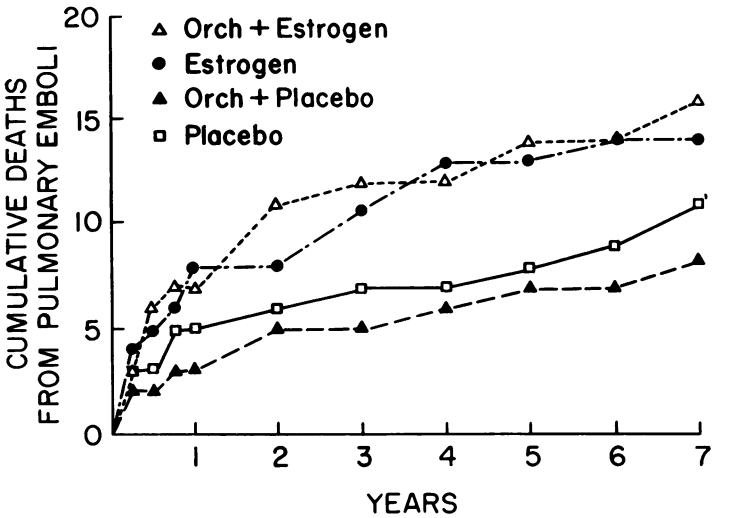

Fig. 5. Deaths due to pulmonary emboli by assigned treatment in Study I (as of April 1970).

the first year; there is very little if any difference after that point.

Even though we concluded that initial treatment with 5.0 mg. DES was, on the whole, not as good as initial treatment with placebo, we found that many placebo patients later benefitted when they were given estrogens to control symptoms caused by their cancer.[2] Our recommendation was that "therapy by estrogen or orchiectomy should be withheld until the symptoms are so severe that they require relief."[3] It should be noted that this conclusion is consistent with the fact that no treatment differences were shown in Stage IV, where symptoms often exist already. In Stage IV relief of symptoms is very important, and may be all that the urologist can offer his patient at present. It was the increased hazard of cardiovascular mortality in the asymptomatic patients of Stages I, II, and III which we wished to emphasize.

When the results of the first V.A. study were published in May 1967,[2] a flurry of criticism ensued. The principal points were: 1) that the dose of estrogen was too high; 2) that the cause of death was determined on the basis of inadequate information; 3) that there was not enough information about the pretreatment cardiovascular status of the patients; and 4) that patients were not always kept on the assigned treatment.

TABLE VI. COMPARISON OF TREATMENTS IN PROSTATE STUDIES I AND II

Stages	*First study*	*Second study*
I and II	Prostatectomy + placebo ←→	prostatectomy + placebo
	Prostatectomy + 5.0 mg DES*	Placebo
III and IV	Placebo ←→	Placebo
	Placebo + orchiectomy	0.2 mg DES*
	5.0 mg DES* + orchiectomy	1.0 mg DES*
	5.0 mg DES* ←→	5.0 mg DES*

*Daily dose of diethylstilbestrol

I have already explained our reason for including patients whose treatment was later changed. The dose of estrogen chosen for the study, though considered too high by some authorities, was certainly in common use in 1960 and was recommended in some texts and articles. The other two points, that cause of death was not determined precisely and that there was inadequate information about the patients' pretreatment cardiovascular status are valid, but they are explained by the fact that the results of this study were as much a surprise to us as to anyone else. We had not anticipated that it would be important to have detailed information about cardiovascular status, or that any thing other than cancer of the prostate would be important as a cause of death in comparing the treatments. Indeed, failure to consider the causes of death was the flaw in much of the previous work done on treatment of this disease.

Determination of cause of death is not easy. Consider the 72-year-old patient with widespread metastases who is confined to bed, develops bronchopneumonia, then dies suddenly of a heart attack. What should we say was his cause of death? Even with an autopsy the problem does not disappear. The autopsy rate in our studies is about 40%; since many of these patients die at home, we can do little to improve this figure. Cause of death is determined by a committee of three or more clinicians who review all deaths independently, then discuss the cases on which they disagree. This committee uses the death certificate, the autopsy report (if an autopsy was performed), the patient's study records, and a summary of the last illness written by the principal investigator. Even if the cause of death is not always precise, this fact would not tend to bias the results since the death–evaluation committee does not know the treatment to which the patient was randomly assigned.

TABLE VII. DEATHS BY STAGE, TREATMENT, AND CAUSE OF DEATH IN PROSTATE STUDY II

Stage	*III*				*IV*			
Treatment	*Placebo*	*0.2 DES*	*1.0 DES*	*5.0 DES*	*Placebo*	*0.2 DES*	*1.0 DES*	*5.0 DES*
No. of patients	75	73	73	73	53	52	55	54
Ca of prostate	6	5	2	3	19	24	14	11
Cardiovascular	12	11	13	23	10	4	7	7
Other causes	8	18	14	3	6	0	4	5
Total deaths	26	34	29	29	35	28	25	23

The second V.A. study of cancer of the prostate was begun in April 1967, even though follow-up for all patients in the first study is being continued for 15 years from the time of entry to the study or until death. The purpose of the second V.A. study was to study different doses of estrogen and to make other changes in the protocol which permitted the collection of much more detailed information about the patients' cardiovascular systems. Table VI compares the treatments in the two studies. Note that in Stages I and II we have also randomized radical prostatectomy and that because of the results of the first study we are no longer treating these patients with estrogen. In Stages III and IV we are studying placebo and three graded doses of estrogen: namely, 0.2, 1.0, and 5.0 mg. daily. The lines with arrows on the ends indicate the treatments which are common to the two studies. In addition, we have measured blood pressure, pulse, EKG, weight, and circulation time, and have determined 12 laboratory values, including some clotting factors and indices of lipid and protein metabolism. The results derived from this study must be regarded as somewhat tentative since the study has not been in progress very long, but let us look at the results so far. Table VII shows the causes of death in Study II by stage and treatment. Looking at the line for cardiovascular deaths for Stage III, we see that there are appreciably more deaths with 5.0 mg. DES than with the other treatments. This result is consistent with the results for Study I. There are not many deaths from cancer yet in any of the treatment groups in Stage III, probably because the average follow-up time for this study is still too short for Stage III cancer to have progressed to a terminal stage. The most interesting point about the data for Stage IV is that both with regard to cancer deaths and all causes of death, it appears that the 1.0 mg. dose of DES is just as effective as the 5.0 mg.

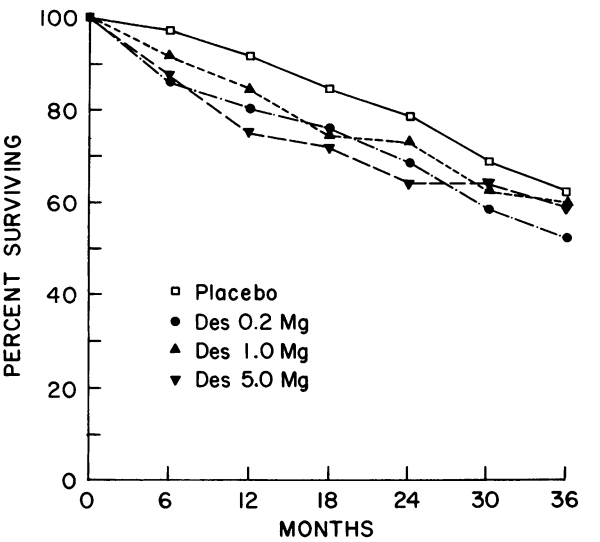

Fig. 6. Prostate study II: survival curves by assigned treatment for Stage III.

dose. In designing this second study we hoped to find a dose of DES which would preserve the beneficial effect of the 5.0 mg. dose on the tumor, without the increased risk of cardiovascular complications or death. So far our data appear to support this hope.

The increased number of deaths in Stage IV in the placebo-treated group requires comment. This effect was not present in the first V.A. study nor is it apparent in Stage III of the present study. There are several explanations for this. First, the investigators have been more reluctant to change the treatment of patients in the second study because their faith in the efficacy of estrogen treatment was shaken by the results of the first study. Yet in Stage IV in the first study we found that patients initially assigned to placebo benefitted when later changed to estrogen. A further explanation for the lowered survival rates for Stage IV placebo patients in the present study lies in the nature of the population of patients. In attempting to reduce the proportion of new patients who are excluded from study, we may have admitted a higher proportion of very sick patients than in the first study. For one thing, the patients in Stage IV no longer have to be considered suitable candidates for orchiectomy. In the first study we found that DES was beneficial for patients with advanced disease. Thus weighting the present study with a higher proportion of more advanced cases would tend to tip the scales against placebo relative to the 5.0 mg. dose.

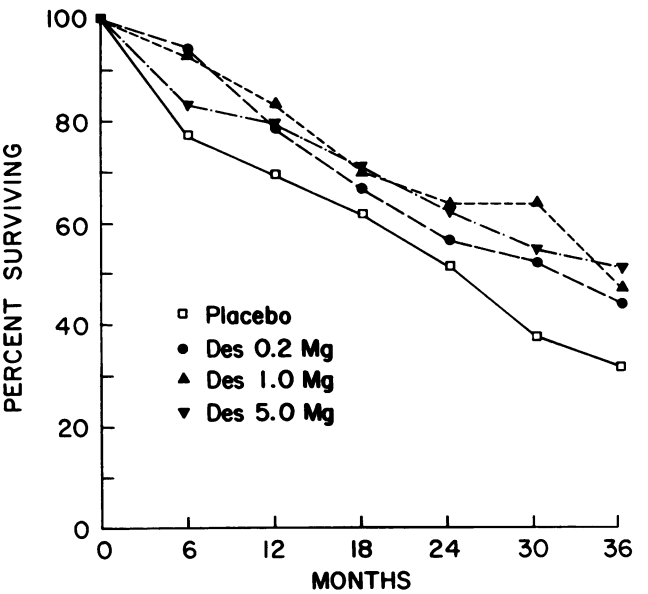

Fig. 7. Prostate study II: survival curves by assigned treatment for Stage IV.

Survival curves for Stage III are shown in Figure 6. The three estrogen doses do not appear very different at this time; indeed, the differences between them are not statistically significant. Placebo appears to be better than any of the estrogen treatments in Stage III, and statistical tests[5] establish its superiority at this time over the 0.2 and 5.0 mg. dose of estrogen.

The survival curves for Stage IV (Figure 7) show placebo to be the worst treatment, just as we saw in the table showing causes of death. The only statistically significant results here are that 0.2 and 1.0 mg. doses of DES are superior to placebo.

Figure 8 shows curves for cardiovascular deaths only for Stage III. The excess hazard of the 5.0 dose of DES is seen more clearly here; it appears to occur principally in the first few months after the patient is placed on study. The three top curves (placebo, 0.2, and 1.0 mg. DES) are all statistically different from that for 5.0 mg. DES but do not differ from each other.

Taking all these rather complex relations into account, our current recommendation would be to use 1.0 mg. DES in preference to 5.0 mg. but to withhold treatment until it is required. That is, we would not

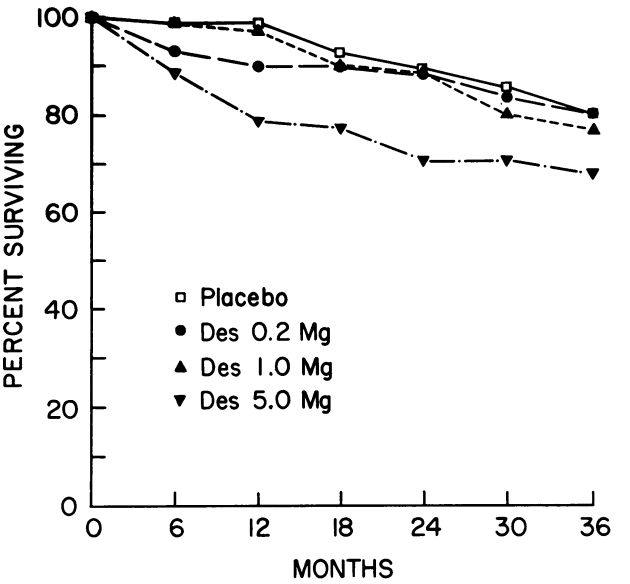

Fig. 8. Prostate study II: survival curves, Stage III: cardiovascular deaths only.

treat Stage III patients until they develop symptoms, and then we would recommend starting them on 1.0 mg. DES daily. In Stage IV we would likewise withhold treatment until the appearance of symptoms, again treating initially with 1.0 mg. DES. These recommendations may be changed as we obtain longer follow-up.

It is still too early to comment on the desirability of radical prostatectomy in Stage I and II patients, but we would not recommend that they be treated with estrogens.

Finally, I should like to report that in 1969 a third V.A. study of cancer of the prostate was begun, and that we are still admitting patients to this study. The treatments for stages I and II are the same as those in Study II but in stages III and IV we are studying Premarin (conjugated "natural" estrogen) and Provera, a progestational agent, in addition to continuing to study the 1.0 mg. dose of DES.

Cancer of the prostate is a slow disease with protean clinical manifestations. Most of the patients are old, and one may expect a high proportion to die of intercurrent diseases. For this reason it has taken a very large, long-term, randomized clinical trial to demonstrate the hazards of a treatment once considered safe. One wonders how many other widely-used treatments for cancer or for other diseases carry

risks that are still unknown because they have not been studied sufficiently.

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